Inhaled Nitroglycerin Versus Inhaled Milrinone in Children with Congenital Heart Disease Suffering from Pulmonary Artery Hypertension

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Objective: **The aim of the present study was to compare the acute effects of inhaled milrinone and inhaled nitroglycerin on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left-to-right shunt) and pulmonary artery hypertension.**

Design: **Randomized clinical trial.**

Setting: **Catheterization laboratory of a tertiary care hospital.**

Participants: **Thirty-five children below the age of 12 years who were suffering from acyanotic congenital heart disease with left-to-right intracardiac shunt and pulmonary artery hypertension (mean PA pressure > 30 mmHg).**

Intervention: **Right-heart catheterization was done using an end-hole balloon wedge pressure catheter. Baseline pulmonary and systemic hemodynamic parameters were recorded for all patients while breathing room air. All patients then underwent pulmonary vasodilator testing with 100% oxygen. Following this, patients were randomized into two groups and received either inhaled milrinone (group M, n = 18) or inhaled nitroglycerin (group N, n = 17) in a 50% air-oxygen mixture. Oximetry data were used to calculate systemic and pulmonary cardiac output based on Fick's principle.**

Results: **Systolic, diastolic, and mean pulmonary artery pressures decreased significantly in both the groups after drug nebulization, while there were no significant changes in systemic pressures. The percentage decrease from baseline in systolic (5.2% *v* 8.6%, $p = 0.43$), diastolic (19.5% *v* 16.8%, $p = 0.19$) and mean (14.9% *v*14.5%, $p = 0.29$) pulmonary artery pressures were comparable in both groups. The pulmonary vascular resistance index (PVRI) decreased from 9.0 ± 3.9 to 2.9 ± 1.7 Wood Units (WU)/m^2 in group M ($p < 0.001$) and from 8.6 ± 3.8 to 3.2 ± 3.3 WU/m^2 in group N ($p < 0.001$). The fall in pulmonary artery pressures after drug nebulization in both groups was comparable to the fall seen with 100% oxygen.**

Conclusion: **Both milrinone and nitroglycerin when given via the inhaled route significantly decrease systolic, diastolic and mean pulmonary artery pressures as well as PVRI without significant effects on systemic hemodynamics. Both the drugs given via inhaled route therefore can offer a good therapeutic choice and can help decrease the high inspired oxygen concentrations needed to treat pulmonary artery hypertensive episodes in perioperative settings.**

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PULMONARY ARTERY HYPERTENSION (PAH) leading to right-heart failure is an important cause of morbidity and mortality in cardiac patients. Successful perioperative management of these patients involves avoidance of factors that can precipitate pulmonary hypertensive crisis as well as use of drugs that can lower pulmonary vascular tone. Traditional therapeutic strategy for pulmonary artery hypertension has consisted of intravenous vasodilators (nitroglycerin, sodium nitroprusside, prostaglandins, phosphodiesterase inhibitors), but their lack of selectivity for pulmonary vasculature leads to systemic side effects, limiting their role in treatment of PAH.[1,2] Recent interest is on the administration of these drugs through the inhalation route so as to selectively target the pulmonary vasculature.

The most commonly used therapy by the inhalation route is nitric oxide (NO), but this is expensive, requires specialized equipment, and there is concern regarding its toxicity.[3,4] Nitroglycerin, a nitric oxide donor drug, has been found to be effective via the inhaled route in reducing PAH in adult cardiac patients undergoing mitral valve surgery.[5] Milrinone, when given via the nebulized route, has also been shown to result in a greater chance of successful weaning from cardiopulmonary bypass in high-risk cardiac patients.[6] Nitroglycerin has been used via the inhaled route in children with PAH but the data are very limited.[7,8] From the above facts, the authors hypothesized that inhaled milrinone and nitroglycerin would significantly reduce pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). In the present study, the authors compared the acute effects of inhaled milrinone and inhaled nitroglycerin on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (CHD) with left-to-right intracardiac shunt and pulmonary artery hypertension.

MATERIALS AND METHODS

After approval from the institute's ethics committee and written informed consent from the parents, 40 children (age < 12 years) with acyanotic CHD (left-to-right intracardiac shunt) with moderate or severe PAH (defined by mean PAP > 30 mmHg) were enrolled in the study. Patients with associated mitral valve disease, severe pulmonary or tricuspid regurgitation, obstructive lesions, severe left ventricular dysfunction, and those already receiving vasodilator treatments were excluded from the study.

Oral chloral hydrate and intramuscular meperidine with promethazine were given for sedation and right-heart catheterization using an end-hole balloon wedge pressure catheter was done under local anesthesia. Baseline heart rate, systolic, diastolic, and mean systemic as well as PAPs, right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP) were calculated for all patients while breathing room air. Blood samples were collected from the superior vena cava (SVC), pulmonary artery (PA), and femoral artery (FA) in heparinized syringes to measure saturation and partial pressure of oxygen. Oxygen consumption (VO_2) was obtained from a standard nomogram routinely used in this cardiac catheterization laboratory, based on age, sex, and heart rate of the child. Pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI), and pulmonary-to-systemic blood flow ratio (Q_p/Q_s) was calculated using standard formulae based

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Table 1. Patient Characteristics

Patient Characteristic	Group M (Milrinone, n = 18)	Group N (Nitroglycerin, n = 17)
Age (months)	48 (12-132)	48 (16-132)
Weight (kg)	11.5 (6-30)	13 (7-20)
Height (cm)	95.5 (62-151)	96 (73-130)
Male:female	11:7	10:7
Congenital heart disease		
VSD	13	12
VSD + ASD	2	2
Partial AVSD	2	1
PDA	1	2

NOTE. Data are expressed as median (range) for age, weight and height.

Abbreviations: VSD, ventricular septal defect; ASD, atrial septal defect; AVSD, atrioventricular septal defect; PDA, patent ductus arteriosus.

on Fick's principle.[9] The authors have taken the oxygen content of the femoral artery (instead of the pulmonary vein) for calculation of Qp and PVRI as all the patients had left-to-right intracardiac shunts without any systemic arterial desaturation.

All patients then received 100% oxygen for 10 minutes using a facemask and Jackson Rees system attached to an anesthesia machine. Hemodynamic and oximetric data were recorded again in a similar manner as described above and this set of data was termed as "post-oxygen data." The patients at this point were randomized into two groups using computer-generated random numbers that were kept in sealed envelopes. They received either nebulized milrinone (group M) or nebulized nitroglycerin (group N) 10 minutes after discontinuation of 100% oxygen (time allowed for hemodynamic parameters to return to baseline). Group M inhaled milrinone in a dose of 50 μg/kg and group N inhaled nitroglycerin in the dose of 50 μg/kg.

The drugs were dissolved with normal saline to make a volume of 3 mL and they were nebulized over a period of 10 minutes with a jet nebulizer using 8 L/min of 50% air-oxygen mixture. After completion of nebulization, a complete set of hemodynamic and oximetric data was recorded again, and this data were termed as "post-milrinone or post-nitroglycerin data." Five patients out of 40 heavily sedated with a $PaCO_2$ of $\geq$ 45 mmHg were excluded from the analysis.

Data analysis was done using SPSS software (SPSS version 15; SPSS, Inc, Chicago, IL). The comparison within each group was carried out by applying repeated measure analysis followed by post hoc comparison by the Bonferroni method. The intergroup comparison at each time point was done by using an unpaired test. A p value of <0.05 was considered to be significant.

RESULTS

The demographics and the clinical diagnosis of the patients receiving milrinone (group M, n = 18) and nitroglycerin (group N, n = 17) were similar (Table 1). Hemodynamic variables in group M and group N are shown in Tables 2 and 3, respectively. After drug nebulization or treatment with oxygen, both groups did not reveal any significant changes in heart rate, systolic, diastolic and mean systemic arterial pressures, RAPs and PCWP while compared with their baseline values. However, the systolic, diastolic and mean PAPs decreased significantly in both groups. The percentage decrease from baseline in systolic (5.2% v 8.6%, $p = 0.43$), diastolic (19.5% v 16.8%, $p = 0.19$) and mean (14.9% v 14.5%, $p = 0.29$) PAPs was comparable in both groups (Fig 1).

After drug nebulization, the PVRI decreased from baseline value of 9.0 ± 3.9 to 2.9 ± 1.7 WU/m^2 in group M ($p < 0.001$) and from 8.6 ± 3.8 to 3.2 ± 3.3 WU/m^2 in group N ($p < 0.001$). The fall in PVRI was comparable in both groups (67.7% in group M and 62.8% in group N, $p = 0.78$) (Fig 2). SVRI deceased from 19.1 ± 7.4 to 15.6 ± 7.6 WU/m^2 in group M ($p = 0.001$) and from 21.3 ± 4.7 to 16.5 ± 3.2 WU/m^2 in group N ($p = 0.001$). The fall in SVRI (18.3% in group M and 22.5% in group N) was small as compared with fall in PVRI ([Group M, 67.7%; Group N, 62.8%]; Fig 2). Pulmonary-to-systemic blood flow ratio (Qp/Qs) increased significantly from

Table 2. Milrinone Group: Systemic and Pulmonary Hemodynamic Variables Expressed as Mean ± SD

Variable	Baseline (1)	Post Oxygen (2)	Post Milrinone (3)	p Value	Post-hoc Comparison (1-2) (1-3) (2-3)
HR (b/min)	113.6 ± 13.7	114.4 ± 12.9	114.9 ± 13.6	0.52	—
SAP (mmHg)	115.0 ± 15.8	111.9 ± 15.7	113.1 ± 14.6	0.14	—
DAP (mmHg)	61.6 ± 12.7	63.1 ± 13.5	62.4 ± 12.2	0.32	—
MAP (mmHg)	80.7 ± 14.5	80.4 ± 14.8	80.5 ± 13.6	0.93	—
SPAP (mmHg)	96.9 ± 17.2	95.4 ± 19.5	92.0 ± 16.3	0.012	(0.99) (0.01) (0.06)
DPAP (mmHg)	48.3 ± 14.1	42.0 ± 15.6	38.9 ± 13.3	<0.001	(0.02) (<0.001) (0.04)
MPAP (mmHg)	67.0 ± 15.4	61.2 ± 16.1	57.1 ± 13.2	<0.001	(0.02) (<0.001) (0.01)
RAP (mmHg)	8.1 ± 3.4	8.1 ± 3.5	8.0 ± 3.1	0.89	—
PCWP (mmHg)	13.1 ± 3.7	13.6 ± 3.7	13.1 ± 3.5	0.32	—
SVRI (Wood.m^2)	19.1 ± 7.4	15.9 ± 9.6	15.6 ± 7.6	0.001	(0.015) (0.001) (0.99)
PVRI (Wood.m^2)	9.0 ± 3.9	3.4 ± 2.3	2.9 ± 1.7	<0.001	(<0.001) (<0.001) (0.04)
Qp/Qs	1.7 ± 0.6	3.8 ± 1.7	3.9 ± 1.6	<0.001	(<0.001) (<0.001) (0.99)

NOTE. p value <0.05 considered significant.

(1-2) Comparison between baseline and values after 100% oxygen.

(1-3) Comparison between baseline and after milrinone.

(2-3) Comparison between values after 100% oxygen and after milrinone.

Abbreviations: HR, heart rate; SAP, DAP, and MAP, systolic, diastolic, and mean systemic arterial pressure, respectively; SPAP, DPAP, and MPAP, systolic, diastolic, and mean pulmonary artery pressure, respectively; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; Qp/Qs, ratio of pulmonary-to-systemic blood flow.

Table 3. Nitroglycerin Group: Systemic and Pulmonary Hemodynamic Variables Expressed as Mean ± SD

Variable	Baseline (1)	Post Oxygen (2)	Post NTG (3)	*p* Value	Post-hoc Comparison (1-2) (1-3) (2-3)
HR (b/min)	115.3 ± 19.2	116.0 ± 18.7	115.5 ± 18.9	0.62	—
SAP (mmHg)	119 ± 17.9	116.7 ± 16.5	117.7 ± 17.0	0.15	—
DAP (mmHg)	66.1 ± 14.8	66.8 ± 14.7	66.4 ± 13.7	0.81	—
MAP (mmHg)	85.2 ± 14.8	84.5 ± 15.2	84.9 ± 14.4	0.77	—
SPAP (mmHg)	105.2 ± 19.6	97.8 ± 16.9	96.4 ± 15.9	<0.001	(0.014) (0.002) (0.73)
DPAP (mmHg)	53.5 ± 16.7	45.8 ± 13.1	44.4 ± 11.4	<0.001	(0.012) (0.004) (0.35)
MPAP (mmHg)	72.3 ± 17.1	64.4 ± 13.6	61.8 ± 12.2	<0.001	(0.007) (0.001) (0.013)
RAP (mmHg)	7.2 ± 2.8	7.0 ± 2.5	7.1 ± 2.8	0.79	—
PCWP (mmHg)	13.1 ± 4.0	12.6 ± 3.7	12.8 ± 3.6	0.14	—
SVRI (Wood.m²)	21.3 ± 4.7	16.4 ± 3.7	16.5 ± 3.2	<0.001	(<0.001) (0.001) (0.99)
PVRI (Wood.m²)	8.6 ± 3.8	3.4 ± 3.4	3.2 ± 3.3	<0.001	(<0.001) (<0.001) (0.09)
Qp/Qs	2.1 ± 0.8	4.6 ± 2.3	4.7 ± 2.1	<0.001	(<0.001) (<0.001) (0.98)

NOTE. p value < 0.05 considered significant.

(1-2) Comparison between baseline and values after 100% oxygen.

(1-3) Comparison between baseline and after milrinone.

(2-3) Comparison between values after 100% oxygen and after milrinone.

Abbreviations: HR, heart rate; SAP, DAP, and MAP, systolic, diastolic and mean systemic arterial pressure, respectively; SPAP, DPAP, and MPAP, systolic, diastolic and mean pulmonary artery pressure, respectively; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; Qp/Qs, ratio of pulmonary-to-systemic blood flow.

1.7 ± 0.6 to 3.9 ± 1.6 in group M ($p < 0.001$) and from 2.1 ± 0.8 to 4.7 ± 2.1 in group N ($p < 0.001$).

The results also showed that milrinone nebulized in a 50% air-oxygen mixture is more efficacious in lowering PAPs compared with 100% oxygen ([$p = 0.06$, $p = 0.04$ and $p = 0.01$ for systolic, diastolic and mean PAPs] [Table 2, paired comparison, b-c]). This superior effect was not seen in group N, where 100% oxygen and nitroglycerin nebulization in a 50% air-oxygen mixture showed a similar efficacy in lowering PAPs. In this group of patients, statistically significant difference was seen only for mean PAPs ($p = 0.013$; Table 3, paired comparison, b-c).

DISCUSSION

The results of this study demonstrated that in patients with congenital heart disease and pulmonary artery hypertension, both inhaled milrinone and inhaled nitroglycerin led to significant decreases in systolic, diastolic, and mean pulmonary artery pressures. The drugs also cause a decrease in PVRI and SVRI, but the effect on SVRI is small compared with the effect on PVRI, highlighting a more selective effect on pulmonary vasculature when given through the inhaled route. These acute changes with inhaled milrinone and nitroglycerin occurred without any significant changes in heart rate, PCWP or systemic pressures.

The large decrease in PVRI (≈70%) in this study was not followed by similar decreases in PAPs (≈15%). It is due to the fact that a fall in PVRI in patients with left-to-right shunts will lead to an increase in pulmonary blood flow which, in turn, can

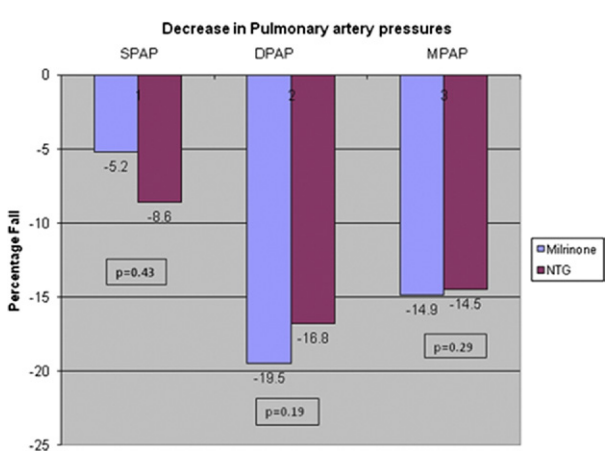

Fig 1. The percentage decrease from baseline in pulmonary artery pressures in milrinone and nitroglycerin groups. SPAP, DPAP, and MPAP, systolic, diastolic, and mean pulmonary artery pressure, respectively. (Color version of figure is available online.)

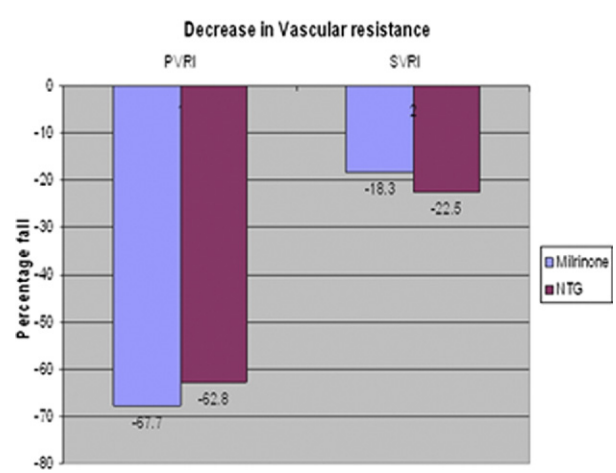

Fig 2. The percentage decrease from baseline in pulmonary and systemic vascular resistance index in milrinone and nitroglycerin groups. SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index. (Color version of figure is available online.)

cause passive distention and recruitment of more pulmonary arteries, thus further lowering the PVRI.[10] This improved pulmonary blood flow will tend to support the PAPs and this can probably explain this smaller percentage fall. The maintenance of systemic pressures even in the presence of a fall in SVRI (≈20%) can be attributed to improved pulmonary blood flow and cardiac output.[11]

These findings are similar to the results of Goyal et al who had used inhaled nitroglycerin in a similar subset of patients with congenital heart disease.[7] These patients had falls in PAPs and PVRI while the investigators did not find any statistically significant drop in SVRI as was seen in this series. This probably can be attributed to the higher dose of inhaled nitroglycerin (50 μg/kg *v* 25 μg/kg) used in this study. The degree of falls in PAPs and PVRI in the patients receiving inhaled nitroglycerin was similar to that seen by Goyal et al, suggesting that an increase in dose of nitroglycerin from 25 μg/kg to 50 μg/kg did not offer any incremental benefit.

Inhaled milrinone at a dose of 50 μg/kg used in this study was based on the bolus intravenous dose. Haraldsson et al also have demonstrated the efficacy of inhaled milrinone in selectively lowering the PVRI compared with SVRI.[12] These authors used milrinone in different concentrations and found that the best response was seen in nebulization concentration of 1 mg/mL (3 mL were nebulized over 10 minutes in an adult cardiac surgical population). This dose was similar to that used in this study. At this dose there was a slight fall in SVR (≈5%), which was not seen with lower concentrations of milrinone (0.25 mg/mL and 0.5 mg/mL). Their study was undertaken in postoperative adult cardiac surgical patients who had undergone coronary artery bypass, mitral valve replacement, or combined procedures. The larger falls in PVRI and SVRI in this series were probably due to the more dynamic nature of PVR in the population with a different pathophysiology contributing to pulmonary hypertension.

The effect of inhaled milrinone was also demonstrated in heart transplant patients with PAH by Sablotizki et al.[13] These authors demonstrated that inhaled milrinone decreased MPAP and PVR only in patients with pulmonary hypertension defined as MPAP above 30 mmHg (no effect of inhaled milrinone was seen in heart transplant patients with normal PAP). The dose of inhaled milrinone used was 2 mg, based on loading dose used in heart transplantation and associated with a 25% fall in PVR and 15% fall in PA pressure.

This investigation demonstrated that NTG and milrinone given via the inhaled route are capable of reducing PVRI. This was accompanied by a small fall in PAP because of the increase in nonrestrictive left-to-right intracardiac shunt. The authors postulate that in the postoperative period, when left-to-right intracardiac shunt has been closed, inhaled nitroglycerin and inhaled milrinone can lead to clinically significant falls in PVRI and PA pressures. Further studies in the settings of postoperative repair will be needed to define the utility of these drugs while given via the inhaled route in preventing pulmonary hypertensive crisis. The authors acquired the baseline values on an F_IO_2 of 0.21, while drug nebulizations were done at F_IO_2 of 0.50. This increased oxygen concentration can confound the interpretation of results and the true beneficial effect of isolated drug nebulization would have been better outlined if nebulization had been done with F_IO_2 of 0.21. However, the authors postulated that a possible future clinical use of these drugs via the inhaled route will be an adjunct in lowering the required oxygen concentrations during the treatment of postrepair pulmonary hypertensive episodes. Such a clinical scenario is unlikely to use a low F_IO_2 of 0.21 and because of this reason, the authors nebulized the drugs in a 50% oxygen mixture.

The standard sedation protocol formulated for children at this institution's cardiac catheterization laboratory was used in this study. Premedication with intramuscular meperidine and promethazine is widely used for sedation of children during cardiac catheterization[14] and has minimal influence on pulmonary hemodynamics if hypercarbia is avoided. In this research, the 5 patients out of 40 who had hypercarbia had received additional intravenous morphine sedation for the procedure and were excluded from the analysis.

The study demonstrates that both inhaled milrinone and inhaled nitroglycerin are similar in efficacy and do not offer any major advantage over each other. Nitroglycerin is, however, cheaper and a more cost-effective drug compared with milrinone. These drugs do not require any specialized equipment as is needed for inhaled NO, which also has the additional risk of toxicity (methemoglobinemia, pulmonary cytotoxicity). One hundred percent oxygen is one of the most potent pulmonary vasodilators, but such high inspired oxygen concentrations for prolonged periods can lead to oxygen toxicity. Therefore, these drugs given via the nebulized route would be beneficial adjuvants for lowering the required oxygen concentrations during perioperative management of pulmonary artery hypertensive episodes.

Limitations of the Study

The authors did not study the duration of effect of inhaled milrinone and inhaled nitroglycerin to avoid multiple blood samples and to avoid undue prolongation of cardiac catheterization time in these children. The exact amount of drug reaching the pulmonary and systemic circulation also was not calculated. Lack of controlled ventilation in the patients could have influenced pulmonary hemodynamics ($PaCO_2$ ranged from 30 to 42 mmHg in this study group, 5 children with $PaCO_2 \geq 45$ mmHg were excluded). Drug nebulization was done with an F_IO_2 of 0.5, which can confound the interpretation of results. The true beneficial effect of isolated drug nebulization would have been better outlined if nebulization had been done with an F_IO_2 of 0.21. VO_2 values were taken from standard normograms, which can produce inaccuracies in calculation of PVRI and SVRI.[9]

The authors have not studied the effect of these drugs on the children with a left-to-right intracardiac shunt and pulmonary hypertension with a $PaCO_2 \geq 45$ mmHg. This is one of the important limitations of the present trial. Further studies are needed on these two inhaled drugs based on the $PaCO_2$ of patients with this pathophysiology to recognize and define the population in which they are most effective.

CONCLUSION

Both milrinone and nitroglycerin given via the inhaled route significantly decrease systolic, diastolic and mean PAPs as well as PVRI without significant effects on systemic hemodynamics. Both drugs given via the inhaled route offer a good therapeutic choice to address pulmonary artery hypertensive episodes in perioperative settings. Additional studies are needed to define the optimal dosing range for both drugs via the inhalation route to treat children with severe pulmonary artery hypertension.

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